What do we need to know about RAVs clinically?

Stefan Zeuzem, MD
University of Frankfurt
Germany
Background

- Resistance associated variants (RAVs) or resistance associated polymorphisms (RAPs) with reduced drug susceptibility are observed in patients with chronic HCV
  - Due to the high replication rate of HCV ($10^{12} / \text{day}$)
  - Error-prone RNA-dependent RNA polymerase ($10^{-4}$ to $10^{-5}$ per copied nucleotide)

- All possible single and double mutants are predicted to be generated multiple times each day

- Not all RAVs are fit enough to persist (but potentially under selection pressure of a respective DAA). Most NS3A RAVs disappear after EoT (HCV1b > HCV1a), while many NS5A RAVs persist

- The level of resistance \textit{in vivo} may differ between a RAV in previously untreated patient and the same RAV selected by a DAA (= TEV) (e.g. due to compensatory mutations)

Rong et al., Sci Transl Med 2010
How to define a RAV?

- **RAV per specific drug or drug class**
  (e.g. resistance against elbasvir or any NS5A inhibitor)

- **Genotypic backbone *in vitro* and *in vivo***
  (e.g. genotype 1a or 1b replicons, other genotypes)

### Table: RAVs in NS5A

<table>
<thead>
<tr>
<th>Group</th>
<th>GT</th>
<th>K24</th>
<th>M28 (L28)†</th>
<th>Q30 (R30)*</th>
<th>L31</th>
<th>P32</th>
<th>S38</th>
<th>H58 (P58)‡</th>
<th>A92</th>
<th>Y93</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1b</td>
<td>-¶</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>L</td>
<td>-¶</td>
<td>D</td>
<td>K</td>
<td>Any</td>
</tr>
<tr>
<td>NS5A Class RAVs</td>
<td>1a or 1b</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
</tbody>
</table>

- †Wild type amino acid at position 28 is M in GT1a and L in GT1b
- *Wild-type amino acid at position 30 is Q in GT1a and R in GT1b.
- ‡Wild type amino acid at position 58 is H in GT1a and P in GT1b
- ¶No EBR RAVs identified at this position

Note that EBR RAVs are a subset of the NS5A class RAVs

Zeuzem et al., Ann Intern Med 2015
Jacobson et al., AASLD 2016
How to define a RAV?

• RAV per specific drug or drug class
  (e.g. resistance against ledipasvir or any NS5A inhibitor)

• Genotypic backbone *in vitro* and *in vivo*
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• Level of reduced susceptibility *in vitro*
  (e.g. any aa change vs >2.5-fold vs >100-fold)
# NS5A RAVs - Overview

<table>
<thead>
<tr>
<th></th>
<th>GT 1a</th>
<th>GT1b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M28T</td>
<td>Q30R</td>
</tr>
<tr>
<td><strong>Ledipasvir</strong></td>
<td>&gt;20x</td>
<td>&gt;100x</td>
</tr>
<tr>
<td><strong>Ombitasvir</strong></td>
<td>&gt;1,000x</td>
<td>&gt;100x</td>
</tr>
<tr>
<td><strong>Daclatasvir</strong></td>
<td>&gt;100x</td>
<td>&gt;1,000x</td>
</tr>
<tr>
<td><strong>Elbasvir</strong></td>
<td>&gt;10x</td>
<td>&gt;10x</td>
</tr>
<tr>
<td><strong>Velpatasvir</strong></td>
<td>&lt;10x</td>
<td>&lt;3x</td>
</tr>
<tr>
<td><strong>Odalasvir</strong></td>
<td>&gt;20x</td>
<td>&lt;10x</td>
</tr>
<tr>
<td><strong>ABT-530</strong></td>
<td>&lt;3x</td>
<td>&lt;3x</td>
</tr>
<tr>
<td><strong>MK-8408</strong></td>
<td>&lt;10x</td>
<td>&lt;10x</td>
</tr>
</tbody>
</table>

EC$_{50}$ fold-change compared to WT replicon

Cheng et al., EASL 2012; Wong et al., AAC 2013; Krishnan et al., AAC 2015; Fridell et al., Hepatology 2011; Liu et al., AAC 2015; Cheng et al., EASL 2013; Patel et al., EASL 2015; Ng et al., CROI 2014; Asante-Appiah et al., AASLD 2014
How to define a RAV?

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  (e.g. resistance against ledipasvir or any NS5A inhibitor)

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- **Level of reduced susceptibility *in vitro***
  (e.g. any aa change vs >2.5-fold vs >100-fold)

- **Methodology of RAV detection (sensitivity threshold)**
  (e.g. deep sequencing with a cut-off at 1% or populations sequencing with a cut-off at 15-25%)
Methodology of RAV detection

<table>
<thead>
<tr>
<th>GT1a Position</th>
<th>LDV RAVs</th>
<th>NS5A Class RAVs</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>G/N/R</td>
<td>G/N/R</td>
</tr>
<tr>
<td>26</td>
<td></td>
<td>E</td>
</tr>
<tr>
<td>28</td>
<td>A/G/T</td>
<td>A/G/T/V</td>
</tr>
<tr>
<td>30</td>
<td>E/G/H/L/K/R/T</td>
<td>C/E/G/H/I/L/K/R/S/T/Y</td>
</tr>
<tr>
<td>31</td>
<td>I/F/M/V</td>
<td>I/F/M/V</td>
</tr>
<tr>
<td>32</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>38</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>58</td>
<td>D</td>
<td>D/L</td>
</tr>
<tr>
<td>92</td>
<td>K/T</td>
<td>K/T</td>
</tr>
<tr>
<td>93</td>
<td>C/F/H/N/S</td>
<td>C/F/H/L/N/R/S/T/W</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GT1b Position</th>
<th>LDV RAVs</th>
<th>NS5A Class RAVs</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td></td>
<td>M</td>
</tr>
<tr>
<td>31</td>
<td>I/F/M/V</td>
<td>I/F/M/V</td>
</tr>
<tr>
<td>32</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>58</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>92</td>
<td>K</td>
<td>K</td>
</tr>
<tr>
<td>93</td>
<td>C/H/N/S</td>
<td>C/H/N/S</td>
</tr>
</tbody>
</table>

Date on file, Gilead
Hongmei Mo, personal communication
Frequency and characteristics of RAVs in treatment-naive and DAA-experienced patients - European RAVs database:

- Serum samples of 3549 European HCV-infected patients
- Population-based sequencing for NS3, NS5A, and NS5B
  - Considered relevant if associated with treatment failure or shown to confer >2-fold changed drug susceptibility in comparison to reference strain

RAVs in SOF/PR and SOF/RBV failures

- No RAVs detected in G1a or G2

**NS5B**

<table>
<thead>
<tr>
<th></th>
<th>DAA-naive (n=706)</th>
<th>SOF/PR; SOF/RBV (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVs in DAA-naive pts</td>
<td>16%</td>
<td>32%</td>
</tr>
<tr>
<td>RAVs in SOF/PR and SOF/RBV pts</td>
<td>(53%)</td>
<td>(40%)</td>
</tr>
</tbody>
</table>

**NS5B**

<table>
<thead>
<tr>
<th></th>
<th>DAA-naive (n=313)</th>
<th>SOF/PR; SOF/RBV (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVs in DAA-naive pts</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>RAVs in SOF/PR and SOF/RBV pts</td>
<td>(0%)</td>
<td>(11%)</td>
</tr>
</tbody>
</table>

EC50 fold change: 1.6 (L159F together with C316N)
EC50 fold change: 1.3

Dietz J, et al. EASL 2016, Barcelona. #PS007

*Double variants were calculated as single RAVs. Thus, sum of single RAVs frequencies is not identical with rate of patients with RAVs.*
Frequency and characteristics of RAVs in treatment-naive and DAA-experienced patients - European RAVs database:

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Frequency and characteristics of RAVs in treatment-naive and DAA-experienced patients - European RAVs database:

**NS5A – DCV/SOF**

RAVs in DCV/SOF versus LDV/SOF failures (G1)

<table>
<thead>
<tr>
<th>RAVs in DAA-naive pts</th>
<th>RAVs in DCV/SOF pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>(13%)</td>
<td>(83%)</td>
</tr>
</tbody>
</table>

| 1% K24R | 8% M28 | 6% A20T/V | 4% Q30 | 67% E/H/L/R | 3% L31M | 17% H58D | 1% A92T | 8% Y93C/F/N |

**EC50 fold change:**

- >1000
- >100

**NS5A – LDV/SOF**

<table>
<thead>
<tr>
<th>RAVs in DAA-naive pts</th>
<th>RAVs in LDV/SOF pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>(13%)</td>
<td>(82%)</td>
</tr>
</tbody>
</table>

| 1% K24R | 2% M28T/V | 7% Q30 | 59% E/H/L/R | 3% L31M | 9% P32L | 2% H58D | 1% A92T | 1% Y93C/F/N |

**EC50 fold change:**

- >100
- >100

**Frequency and characteristics of RAVs in treatment-naive and DAA-experienced patients - European RAVs database:**

**G1a**

RAVs in DAA-naive pts

<table>
<thead>
<tr>
<th>RAVs in DAA-naive pts</th>
<th>RAVs in DCV/SOF pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>(20%)</td>
<td>(82%)</td>
</tr>
</tbody>
</table>

| 9% L28V | 2% R30H | 73% L31M | 4% A92T | 7% Y93H |

**EC50 fold change:**

- 2–10
- 20–100

**G1b**

RAVs in DAA-naive pts

<table>
<thead>
<tr>
<th>RAVs in DAA-naive pts</th>
<th>RAVs in LDV/SOF pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>(20%)</td>
<td>(93%)</td>
</tr>
</tbody>
</table>

| 9% L28V | 3% R30H | 40% L31M | 4% A92T | 7% Y93H |

**EC50 fold change:**

- 2–100
- >100

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*Double variants were calculated as single RAVs. Thus, sum of single RAVs frequencies is not identical with rate of patients with RAVs.
Frequency and characteristics of RAVs in treatment-naive and DAA-experienced patients - European RAVs database:

RAVs in DCV/SOF versus LDV/SOF failures (G3 & 4)

**G3**
- **NS5A – DCV/SOF**
  - RAVs in DAA-naive pts: (9%) (DAA-naive n=313)
  - RAVs in DCV/SOF pts: (95%) (DCV/SOF n=21)

- **NS5A – LDV/SOF**
  - RAVs in DAA-naive pts: (9%) (DAA-naive n=313)
  - RAVs in LDV/SOF pts: (7%) (LDV/SOF n=15)

**G4**
- **Frequency and characteristics of RAVs**
  - **NS5A – DAA-naive**
    - L28M: (66%) (DAA-naive n=99)
    - L30R/S: (100%) (DCV/SOF n=2)

- **EC50 fold change**
  - 2–10

**EC50 fold change:**
- >1000

Dietz J, et al. EASL 2016, Barcelona. #PS007
Frequency and characteristics of RAVs in treatment-naive and DAA-experienced patients - European RAVs database:

RAVs in 3D failures

**NS3**
- RAVs in DAA-naive pts: 34%, 1%, 28%, <1%, 0% (DAA-naive n=766, 3D n=18)
- RAVs in 3D pts: 39%, 6%, 28%, 4%, <1% (DAA-naive n=766, 3D n=18)

**NS5A**
- RAVs in DAA-naive pts: 1%, <1%, 6%, 4%, <1%, 6% (DAA-naive n=766, 3D n=18)
- RAVs in 3D pts: 53%, <1%, <1%, <1%, <1%, 6% (DAA-naive n=766, 3D n=18)

**NS5B**
- RAVs in DAA-naive pts: 3%, 1% (DAA-naive n=766, 3D n=18)
- RAVs in 3D pts: 6%, 13% (DAA-naive n=766, 3D n=18)

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**G1a**
- EC50 fold change: 10–100
- RAVs in DAA-naive pts: 34%, 1%, 11%, 1%, 1%, <1% (DAA-naive n=706, 3D n=9)
- RAVs in 3D pts: 39%, 0%, <1%, <1%, <1%, <1% (DAA-naive n=706, 3D n=9)

**G1b**
- EC50 fold change: 2–10
- RAVs in DAA-naive pts: <1%, <1%, <1%, <1%, <1%, <1% (DAA-naive n=706, 3D n=9)
- RAVs in 3D pts: <1%, <1%, 78% (DAA-naive n=706, 3D n=9)

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Dietz J, et al. EASL 2016, Barcelona. #PS007
How to define a RAV?

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  (e.g. resistance against ledipasvir or any NS5A inhibitor)

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• Methodology of RAV detection (sensitivity threshold)
  (e.g. deep sequencing with a cut-off at 1% or populations sequencing with a cut-off at 15-25%)

• Impact of RAVs on SVR rates
  (e.g. combination partner, treatment duration, stage of disease)
Simeprevir + Sofosbuvir in GT1a-infected patients (TN+TE): Impact of the NS3 RAV Q80K

Kwo et al., OPTIMIST-1, EASL 2015; Lawitz et al., OPTIMIST-2, Hepatology 2015

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**Tx duration** | 12 weeks
---|---
**Cirrhosis** | No
**Q80K frequency** | 40%
Simeprevir + Sofosbuvir in GT1a-infected patients (TN+TE): Impact of the NS3 RAV Q80K

<table>
<thead>
<tr>
<th>Tx duration</th>
<th>8 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Q80K frequency</td>
<td>42%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Kwo et al., OPTIMIST-1, EASL 2015; Lawitz et al., OPTIMIST-2, Hepatology 2015
Simeprevir + Sofosbuvir in GT1a-infected patients (TN+TE): Impact of the NS3 RAV Q80K

Kwo et al., OPTIMIST-1, EASL 2015; Lawitz et al., OPTIMIST-2, Hepatology 2015
SVR12 Rates by Treatment Regimen (LDV/SOF) and Duration: Patients without Cirrhosis

Studies included for analysis:

Sensitivity threshold at 1% (deep sequencing)

Zeuzem et al., AASLD 2015
SVR12 Rates by Treatment Regimen (LDV/SOF) and Duration: TN Patients with Cirrhosis

Studies included for analysis:
- **LDV/SOF 24 Wks**: GS-US-337-0102 (ION-1), GS-US-334-1274 (Bleeding Disorder)

Sensitivity threshold at 1% (deep sequencing)

Zeuzem et al., AASLD 2015
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- **Impact of RAVs on SVR rates**
  (e.g. combination partner, treatment duration, stage of disease)
Grazoprevir + Elbasvir for 12 wks in TN/relapse GT-1a patients: Impact of NS5A RAVs on SVR rates

Population Sequencing

- EBR RAVs
  - No RAVS: 414/438 (95%)
  - Patients without RAVs: 405 (98%)
  - Patients with RAVs: 14 (35%)
- NS5A Class RAVs
  - No RAVS: 352/438 (80%)
  - Patients without RAVs: 345 (98%)
  - Patients with RAVs: 74 (20%)

Deep Sequencing at 1% Sens. Threshold†

- EBR RAVs
  - No RAVS: 396/439 (90%)
  - Patients without RAVs: 389 (98%)
  - Patients with RAVs: 31 (8)
- NS5A Class RAVs
  - No RAVS: 289/439 (65%)
  - Patients without RAVs: 284 (98%)
  - Patients with RAVs: 136 (31)

PREVALENCE

- EBR RAVs: 98% ± 5%
- NS5A Class RAVs: 86% ± 20%

SVR12

- Patients without RAVs: 98%
- Patients with RAVs: 72%

Jacobson et al., AASLD 2015

1 NGS with 1% ST supplemented by Population Sequencing when NGS not available. † One GT1a was missing baseline population sequencing data but had baseline NGS data
EBR RAV List = For GT1a: M/L28T/A/G, Q/R30E/H/R/G/K/L/D, L31M/V/F, H58D, or Y93C/H/N/S
NS5A Class RAV List = Any variant from reference strain at NS5A position 24, 28, 30, 31, 32, 38, 58, 92 or 93
Effect of RAVs at Specific Baseline Positions on Likelihood to Achieve SVR$_{12}$

**GT1a-Infected TN/TE Subjects given EBR/GZR 12 weeks (no RBV)**

<table>
<thead>
<tr>
<th>RAV Position</th>
<th>SVR12 Subjects with RAVs (1% ST NGS)</th>
<th>SVR12 Subjects With RAVs (Population Sequencing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>15/18 (83.3%)</td>
<td>4/4 (100.0%)</td>
</tr>
<tr>
<td>28</td>
<td>61/68 (89.7%)</td>
<td>29/33 (87.9%)</td>
</tr>
<tr>
<td>30</td>
<td>14/23 (60.9%)</td>
<td>4/10 (40.0%)</td>
</tr>
<tr>
<td>31</td>
<td>15/23 (65.2%)</td>
<td>5/13 (38.5%)</td>
</tr>
<tr>
<td>32</td>
<td>1/1 (100.0%)</td>
<td>--</td>
</tr>
<tr>
<td>38</td>
<td>9/9 (100.0%)</td>
<td>--</td>
</tr>
<tr>
<td>58</td>
<td>75/77 (97.4%)</td>
<td>48/49 (98.0%)</td>
</tr>
<tr>
<td>92</td>
<td>6/6 (100.0%)</td>
<td>3/3 (100.0%)</td>
</tr>
<tr>
<td>93</td>
<td>9/14 (64.3%)</td>
<td>5/8 (62.5%)</td>
</tr>
</tbody>
</table>

NGS using 1% ST supplemented by Population Sequencing when NGS not available
NS5A Class RAV List = Any variant from reference strain at NS5A position 24, 28, 30, 31, 32, 38, 58, 92 and 93
Grazoprevir + Elbasvir for 12 wks in TN/relapse GT-1b patients: Impact of NS5A RAVs on SVR rates

**Population Sequencing**
- EBR RAVS: No RAVS: 220/265 (83%), 17% RAVS
- NS5A Class RAVS: No RAVS: 184/265 (69%), 31% RAVS

**Deep Sequencing at 1% Sens. Threshold†**
- EBR RAVS: No RAVS: 211/265 (80%), 20% RAVS
- NS5A Class RAVS: No RAVS: 172/265 (65%), 35% RAVS

**SVR12**
- Patients without RAVs: 100%, 99%, >99%, 99%
- Patients with RAVs: 98%, 98%, 98%, 99%

1% NGS ST supplemented by Population Sequencing when NGS not available

EBR RAV List = For GT1b: P32L, P58D or A92K or any variant at NS5A position 28, 30, 31 or 93
NS5A Class RAV List = Any variant from reference strain at NS5A position 24, 28, 30, 31, 32, 38, 58, 92 or 93

Jacobson et al., AASLD 2015
Grazoprevir + Elbasvir for 12 wks in non-responder GT-1a patients: Impact of NS5A RAVs on SVR rates

Population Sequencing

EBR RAVS

No RAVS: 61/68 (90%)

10%

97%

59/61

29%

27

Population sequencing

NS5A Class RAVS

No RAVS: 54/68 (79%)

21%

96%

52/54

64%

9

64%

14

Deep Sequencing at 1% Sens. Threshold†

EBR RAVS

No RAVS: 59/68 (87%)

13%

97%

57/59

44%

4

45

31%

NS5A Class RAVS

No RAVS: 47/68 (69%)

31%

96%

45/47

76%

16

21

Patients without RAVs

Patients with RAVs

†NGS 1% ST supplemented by Population Sequencing when NGS not available. ‡ One GT1a was missing baseline population sequencing data but had baseline NGS data

EBR RAV List = For GT1a: M/L28T/A/G, Q/R30E/H/R/G/K/L/D, L31M/V/F, H58D, or Y93C/H/N/S

NS5A Class RAV List = Any variant from reference strain at NS5A position 24, 28, 30, 31, 32, 38, 58, 92 or 93

Jacobson et al., AASLD 2015
Grazoprevir + Elbasvir + RBV for 16/18 wks in NR GT-1a patients: Impact of NS5A RAVs on SVR rates

Population Sequencing

- **EBR RAVs**
  - No RAVS: 51/52 (98%)
  - 2%

- **NS5A Class RAVs**
  - No RAVS: 44/52 (85%)
  - 15%

Deep Sequencing at 1% Sens. Threshold‡

- **EBR RAVs**
  - No RAVS: 48/52 (92%)
  - 8%

- **NS5A Class RAVs**
  - No RAVS: 38/52 (73%)
  - 27%

**SVR12**

- EBR RAVs:
  - 51/51 (100%)
  - 1%

- NS5A class RAVs:
  - 44/44 (100%)
  - 8%

**PREVALENCE**

- 100% 100% 100% 100%

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† NGS 1% ST supplemented by Population Sequencing when NGS not available. ‡ One GT1a was missing baseline population sequencing data but had baseline NGS data

EBR RAV List = For GT1a: M/L28T/A/G, Q/R30E/H/R/G/K/L/D, L31M/V/F, H58D, or Y93C/H/N/S

NS5A Class RAV List = Any variant from reference strain at NS5A position 24, 28, 30, 31, 32, 38, 58, 92 or 93

Jacobson et al., AASLD 2015
How to define a RAV best clinically?

- RAVs (single and combination) per specific drug
- Genotypic backbone *in vitro* and *in vivo*
- Level of reduced susceptibility *in vitro* >100-fold
- Sensitivity threshold at 15-25% (population sequencing)
- Impact of RAVs on SVR rates in defined patient population and a defined regimen (DAA combination, treatment duration)
- and there is even more complexity .........
Y93H and IL28B CC prevalence by region

Prevalence of IL28B CC (%)

<table>
<thead>
<tr>
<th>Region</th>
<th>North America</th>
<th>Europe</th>
<th>Oceania</th>
<th>Asia Pacific</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
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<td>30</td>
<td>22</td>
<td>22</td>
<td>360</td>
<td>597</td>
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<tr>
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</tbody>
</table>

Prevalence of Y93H (%)

<table>
<thead>
<tr>
<th>Region</th>
<th>North America</th>
<th>Europe</th>
<th>Oceania</th>
<th>Asia Pacific</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1a/b</td>
<td>4</td>
<td>8</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>144</td>
<td>73</td>
<td>21</td>
<td>104</td>
<td>597</td>
</tr>
<tr>
<td>3262</td>
<td>929</td>
<td>360</td>
<td>597</td>
<td></td>
</tr>
</tbody>
</table>

Zeuzem et al., AASLD 2015
Association of Y93H and IL28B genotype

5,148 GT1 patients in Gilead HCV clinical trials with both NS5A sequencing and IL28B genotype data

Zeuzem et al., AASLD 2015
SVR12 rates by Y93H or any NS5A RAV and IL28B genotype

Studies included for analysis:

Zeuzem et al., AASLD 2015
SVR12 Rates by Treatment Regimen and Y93H/IL28B: Patients without Cirrhosis

<table>
<thead>
<tr>
<th>Study ID</th>
<th>LDV/SOF 8 Weeks TN &lt; 6M</th>
<th>LDV/SOF 12 Weeks TN</th>
<th>LDV/SOF 12 Weeks TE</th>
</tr>
</thead>
<tbody>
<tr>
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<td>3 3 31 1 102 105</td>
<td>51 239 23 468 479</td>
<td>15 85 11 266 273</td>
</tr>
<tr>
<td></td>
<td>100 100 100 97</td>
<td>100 100 100 98</td>
<td>94 100 97</td>
</tr>
</tbody>
</table>

Studies included for analysis:
It is useful to detect RAVs?

- There is no “YES” or “No” answer
- First and most important: Methodology for detection of RAVs must standardized (and automated)
- Pharmaceutical industry must fully publish available RAV data in collaboration with academia
- Usefulness of RAV testing will be patient population and treatment regimen dependent
- RAV testing most likely not required in patient populations with SVR rates > 99%
- RAV testing most likely be clinical useful and cost-effective in population with suboptimal SVR rates (definition < 95% / < 90%?) & if population large enough
  - Regimens w/o a very high barrier to resistance drug
  - Treatment-experienced patients (in particular when exposed to DAAs)
  - Patients with cirrhosis
  - When the shortest possible treatment duration is economically important
- IL28B CC genotype is significantly associated with a higher prevalence of Y93H. This association is functionally not yet understood
- The relevance of (in particular NS5A) RAVs, baseline HCV RNA levels, and IL28B genotype on treatment outcome requires further intensive clinical research
Treatment decisions in patients with RAVs

- Switch drug class (exception: nucleosidic polymerase inhibitors)
- Treat longer (up to 24 weeks)
- Add ribavirin
- Use triple therapies (NI + PI + NS5A-Inhibitor)
- Second generation PIs and NS5A-Inhibitors (e.g. Glecaprevir, Pibrentasvir)
- Peginterferon (??)